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Blomstrand Lethal Osteochondrodysplasia

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We present the clinical, roentgenographic, and histologic abnormalities in a stillborn infant with Blomstrand osteochondrodysplasia. Parental consanguinity and multiplex occurrence in the patients' sibship confirm the hypothesis of autosomal recessive inheritance of this monogenic lethal entity. The unknown genetic defect interferes severely with skeletal growth through lack of chondrocyte multiplication and apparent uncoupling of the processes of enchondral ossification and skeletal growth.

KEY WORDS: Blomstrand type osteochondrodysplasia, lethal neonatal dwarfism, non-immune hydrops, advanced skeletal age

INTRODUCTION

Over 16 years ago we observed a stillborn girl with a then unknown lethal osteochondrodystrophy. The condition was characterized by increased bone density and advanced bone age and was described subsequently by Blomstrand et al. [1985] and assigned a preliminary nosologic classification by Spranger [1989]. Here we record the clinical, roentgenographic, and histologic changes in one of affected sibs with this lethal osteochondrodysplasia. Parental consanguinity and multiplex occurrence provide evidence for autosomal recessive inheritance.

CLINICAL REPORTS

Patient 1

D.G.F, stillborn at 31 weeks of gestation, was the result of the 4th pregnancy of a G4P3 32-year-old mother and 32-year-old father, who were first cousins once removed. Polyhydramnios was apparent only a few days before delivery. The proposita was an extremely hydropic infant with a length of 33 cm and a weight of 2,800 g (Fig. 1). The edematous, immature placenta weighed 650 g. Edema grotesquely distorted the face, hypoplastic nose (Fig. 2A) and the small apparently low-set ears (Fig. 2B). The thoracic cage was hypoplastic and narrow, the abdomen quite prominent. The limbs were extremely short with hands and feet the best defined parts (Fig. 2C,D). Edema distorted their unusual proportions.

Fig. 1 Stillborn female fetus; grotesque hydropic deformation of facial and body configuration; short and narrow thorax; prominent abdomen; extreme shortness of limbs.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

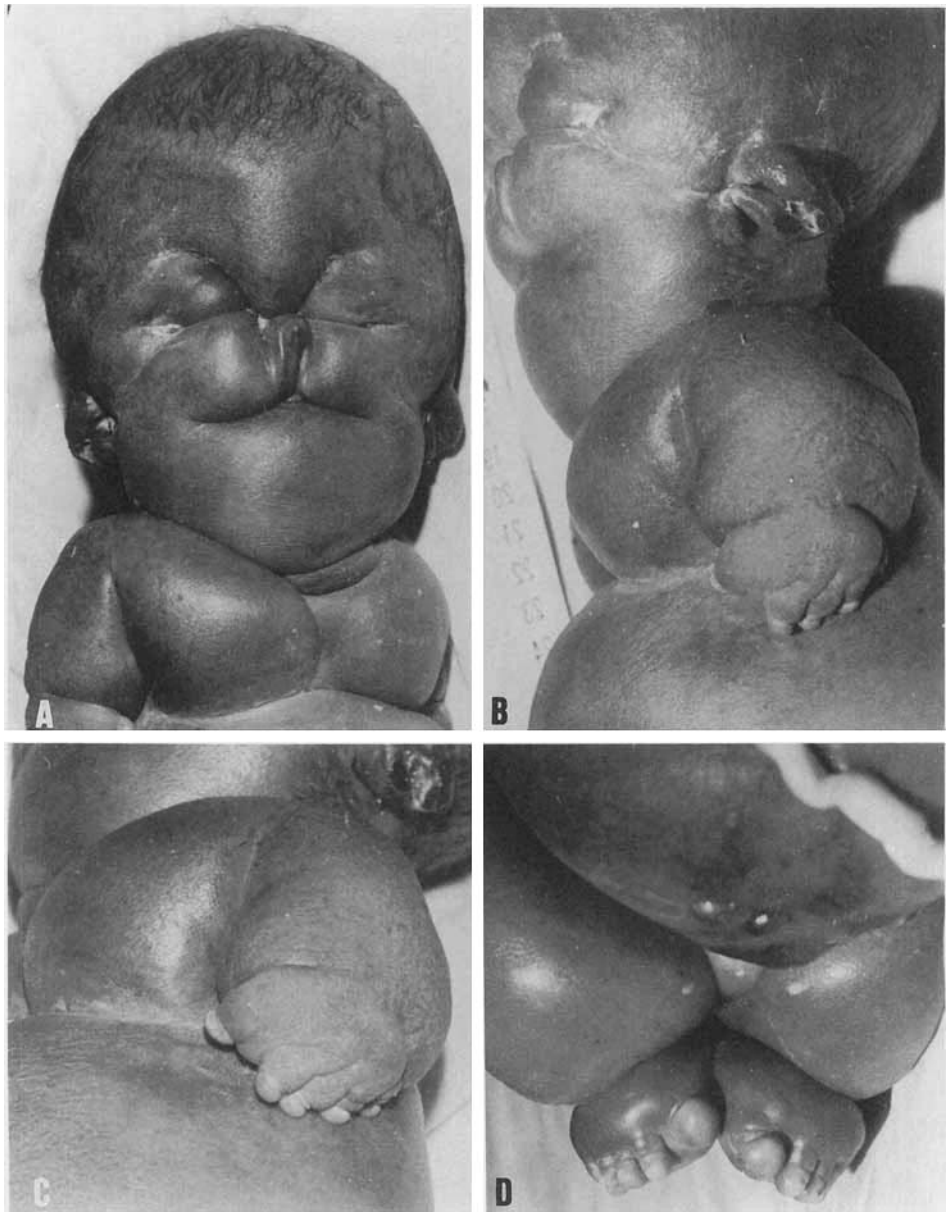


Fig. 2. **A:** Soft tissue edema distorts facial structures and obscures the hypoplastic nose, palpebral fissures and lips. **B:** Apparently low-set small left auricle; shortness more extreme in arms than in hands; narrow short thoracic cage. **C:** Fingers and nails discernible, rhizo- and mesomelic shortness of the upper limbs notwithstanding; hydropic deformation of soft tissue anatomy. **D:** Similarly extreme shortness lower limbs; feet and toes less involved.

Patient 2

Several years earlier the second pregnancy in this family had also been complicated by hydramnios in the last trimester. It resulted in the stillbirth of a male foetus with manifestations nearly identical to these in the proposita. Unfortunately no data other than a gross clinical description were available. The pedigree of this family is shown in Figure 3.

RESULTS OF ADDITIONAL EXAMINATIONS

Roentgenographic Data (Fig. 4A,B)

Generalized soft tissue edema was readily apparent in addition to the pronounced hyperdensity of the skeleton and its markedly advanced ossification. Seven carpal and tarsal bones were discernible but no epiphyses could be seen in the long bones. The facial bones, including the mandible, were small. The base of the skull

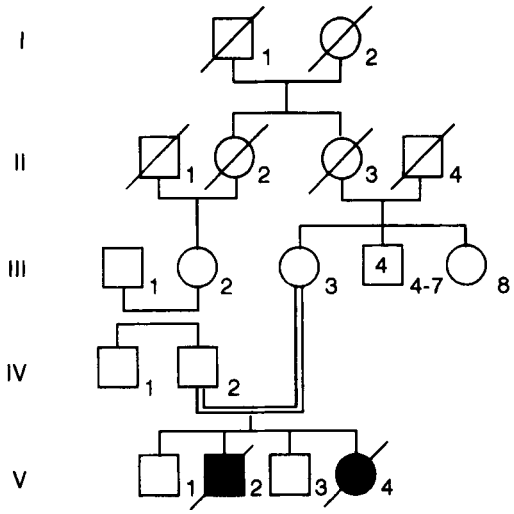


Fig. 3. Pedigree of D.G. family. Father (IV-2) and mother (III-3) are first cousins once removed. Besides the proposita (V-4), V-2 (patient 2) was also stillborn following polyhydramnios; phenotypic appearance similar to that in proposita.

was short and narrow. There was a post-mortem artefactual disarticulation in the craniocervical region. The hypoplastic vertebrae were bowtie-shaped and the scapulae fully ossified. Contrary to the long bones in the limbs, the boomerang-shaped clavicles were relatively long. The short ribs with horizontal orientation were wide anteriorly. The dumb-bell shape of the long bones in the limbs was due to extreme diaphyseal shortness and constriction and marked flare of the metaphyseal ends.

Autopsy

The extreme hydrops was shown to contribute considerably to the deformation of the eyelids, the nose and the hypoplastic pinnae with normally patent external auditory canals. Edema also severely deformed limbs, thoracic cage and abdomen. No anomaly of any internal organ, including the heart and large vessels, was detected. There was impressive edema of all viscera and accumulation of serous fluid in the pleural, pericardial, and peritoneal cavity. The laryngeal bones were already ossified. The spine was straight with the vertebrae easily identifiable. Sternum and ribs, already much ossified, formed a narrow, rigid thoracic cage. The impression of an enlarged head was a false one created by the extensive subcutaneous edema. The skull was rather small instead and was composed of unusually hard calvarial bones. The fontanelles were of normal size for gestational age. The meninges appeared normal but edematous. Already partially autolysed at the time of autopsy, the brain's macroscopic appearance was considered normal for gestational age.

Shortness of the four limbs was extreme but almost proportional. Prior to histologic fixation, contact radiographs were made of the long bones in the right limbs.

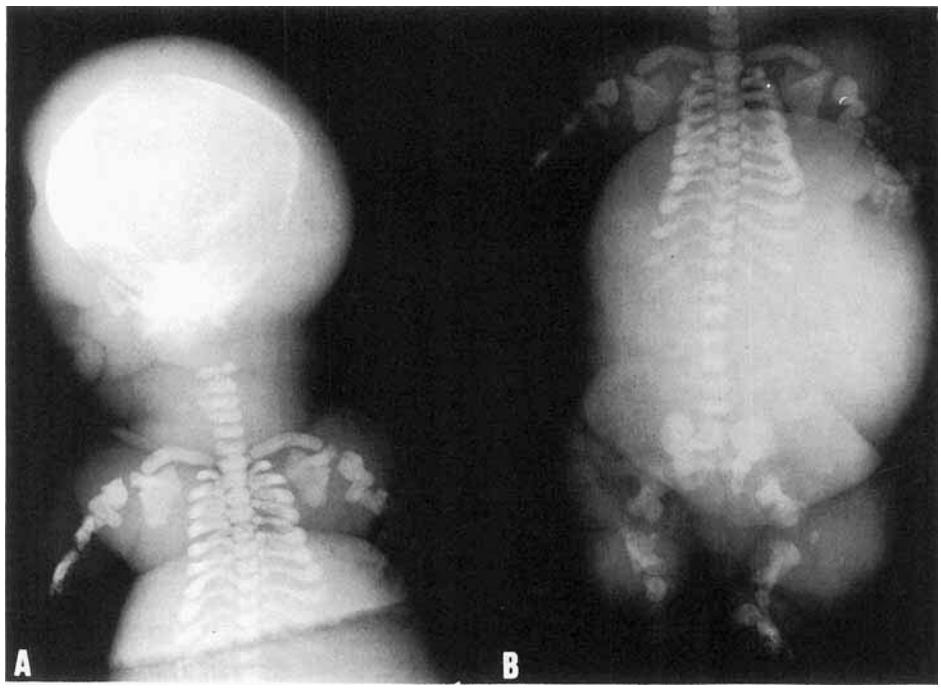


Fig. 4. Post-mortem radiographs of proposita. **A:** Head, neck, and upper thorax: generalized hydrops; artefactual separation of skeleton of head and cervical spine. Small facial skeleton, narrow skull base; increased bone density; bowtie-shaped vertebrae; plump but rather long clavicles with boomerang shape; completely ossified scapulae; extreme shortness of hyperdense ribs. **B:** Trunk and limbs: horizontal orientation of short ribs with spatulated ends; hypoplastic hyperdense pelvic bones; dumbbell-shaped long bones in limbs, with extreme metaphyseal widening and diaphyseal constriction; seven carpal and all tarsal bones ossified, but no secondary epiphyseal centers of ossification visualized in long bones.

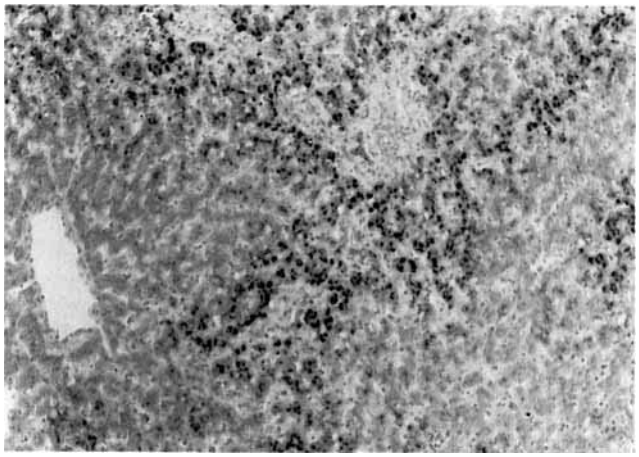


Fig. 5. Iron deposits in hepatocytes, mainly in the periportal areas. Cells near centrolobular veins remain unaffected by this storage phenomenon (×112; Prussian blue stain).

Extreme shortness, increased bone density, and absence of metaphyseal growth plates were confirmed.

Histologic Study

Except for the accumulation of iron containing material (siderosis) in the periportal areas of the liver (Fig. 5), no histological abnormalities were detected in the viscera. Extramedullary hematopoiesis was not considered excessive for fetal age. However it was prominent within the medullary cavity in the ossified laryngeal bone. The marrow cavity of the long bones was either not visible or severely reduced in size (Fig. 6).

Enchondral ossification was advanced and abnormal as epiphyseal and metaphyseal ossification centers in the long bones appeared to have fused already (Fig. 6). Thus, both ends of all long bones in this patient were called an epiphyseal region. Both cells and matrix in the narrow remnants of resting cartilage were histologically normal except for occasional enlarged lacunae around a few resting chondrocytes in the immediate vicinity of the remaining center of enchondral ossification (Figs. 7–9). As the zones of chondrocyte proliferation and column formation were lacking, the zones of chondrocyte hypertrophy and degeneration, themselves poorly defined, narrow and irregular, were immediately adjacent to the resting cartilage. In the remaining area of enchondral ossification intercellular cartilagenous matrix appeared rather abundant, but its transition into osseous tissue was severely disorganized. Ingrowth of capillaries, osteoclastic activity, and the process of bone formation itself appeared morphologically unaltered. However, the resulting trabeculae were wide, tortuous, extremely short, and irregularly oriented (Fig. 7–9).

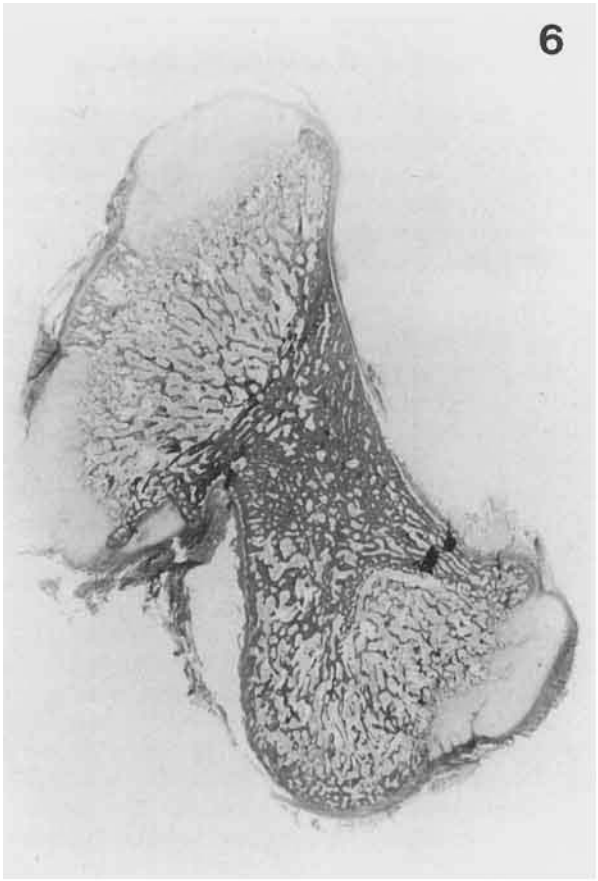
DISCUSSION

The sudden occurrence at 31 weeks of polyhydramnios and the subsequent stillbirth, a common outcome of pregnancy in the lethal osteochondrodysplasias (LOCs), was unanticipated in this family as prenatal ultrasonography was not available in 1979 and an explanation of the previous fetal loss had neither been sought nor provided. The post-mortem total body radiograph led to the diagnosis of a distinct LOC which at the time had not been described. It has since been recognized to be identical to the condition in the patient with lethal congenital dwarfism with accelerated skeletal maturation reported by Blomstrand et al. [1985]. The same LOC was also observed by Spranger or Maroteaux, called Blomstrand chondrodysplasia and given a preliminary classification among the group of Kniest-like disorders in the published list of LOCs [Spranger, 1989; Spranger and Maroteaux, 1990]. Blomstrand type chondrodysplasia is sufficiently different from the Kniest-like chondrodysplasias in order to predict the transient nature of this accommodation. Histologically the Swiss-cheese type resting cartilage is absent unless the occasional enlarged lacunae around resting chondrocytes in the immediate vicinity of the epiphyseal regions in long bones are interpreted in this manner. The patient reported by Young et al. [1993] had many roentgenographic anomalies similar, if not identical, to the ones described in Blomstrand chondrodysplasia of which she is also a probable example. The degree of skeletal hyperdensity was similar, but the advance of skeletal age and the shortness, of all long bones, particularly the ones in the lower limbs, was less pronounced than in the patient here presented.

As noted in all previously reported cases, this infants parents also were consanguineous. This fact, in addition to the probable multiplex occurrence in this sibship, provides strong confirmation of the autosomal recessive mode of inheritance of Blomstrand type lethal chondrodysplasia. Because each one of the patients so far reported has had consanguineous parents, the gene mutation must have a low population frequency.

Bony hyperdensity and impressive advancement of the skeletal age are most prominent and characteristic of this lethal chondrodysplasia. The former manifestation was at least partly explained by the post-mortem histological study of bone tissue. In the extremely short long bones, the much widened, tortuous, and coarse diaphyseal trabeculae left almost no marrow space. Therefore, multiplication and differentiation of precursor blood cells was most likely interfered with as a consequence: severe fetal anemia and subsequent cardiac and circulatory failure led to fetal non-immune hydrops. The latter was probably compounded by the mechanical factors known to impede the normal flow of amniotic fluid and to contribute to third trimester polyhydramnios and generalized soft tissue edema in a large proportion of fetuses with any type of LOC.

The advancement of skeletal age at 31 weeks of gestation was extreme in this stillborn infant as nearly all carpal and tarsal bones were ossified and all epiphyseal centers of ossification had fused with the corresponding diaphyseal parts in the long bones. No metaphyseal growth plates could be discerned either radiologically or histologically. Histologically the multiplication of reserve chondrocytes was very defi-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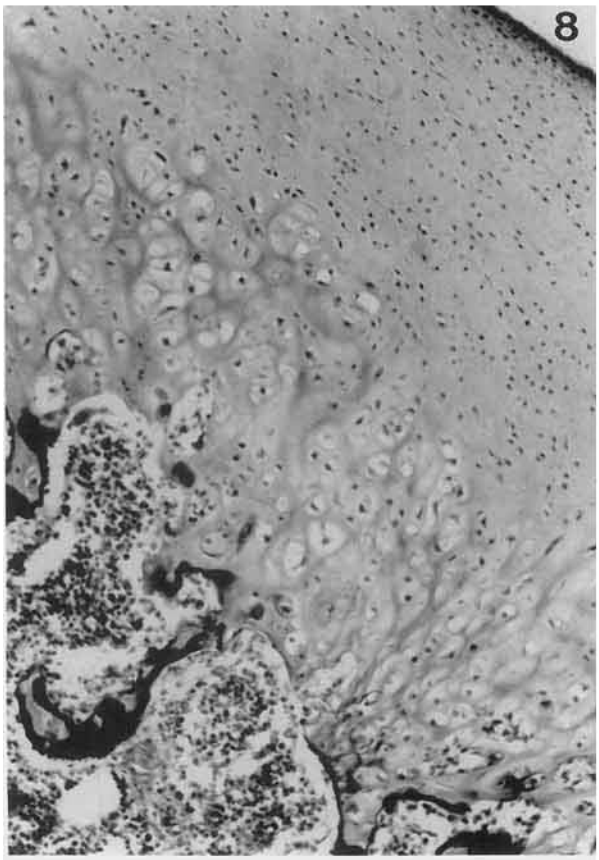
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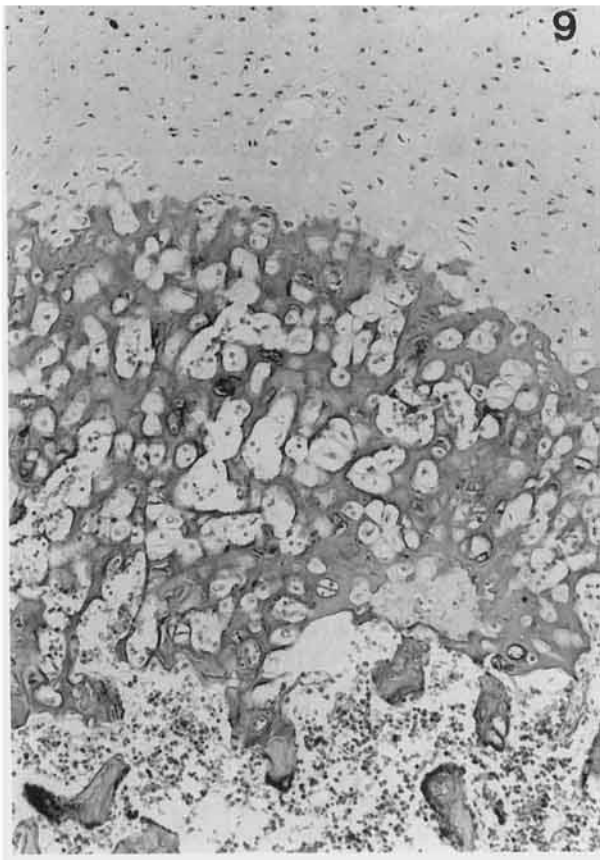
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cient, the zone of chondrocytic proliferation lacking almost completely. Contrary to the expected anthropometric result of normal enchondral bone formation, the precipitous ossification in this condition appeared to be almost completely uncoupled from the phenomenon of skeletal and body growth.

Fig. 6. Low power (×4) view of the longitudinally sectioned right femur; haematoxylin-eosin (H & E), reduced amount of epiphyseal resting cartilage; separate secondary ossification and growth plates not discernible; greatly advanced but disorderly ossification with tortuous preliminary bone and compact cancelous bony trabeculae partly explaining increased bone density and resulting in apparent absence or significantly reduced bone marrow space.

Fig. 7. Right femur, section through proximal epiphyseal region: normal appearing chondrocytes and matrix in narrow remnants of resting cartilage; severely abnormal enchondral ossification; lack of cartilaginous zones of proliferation and columnization; short, tortuous, broad bony trabeculae (×64; Masson trichrome stain).

Fig. 8. Epiphyseal region of right femur; highly abnormal and irregular enchondral ossification; poorly defined zones of chondrocyte hypertrophy and degeneration immediately adjacent to resting cartilage; some resting chondrocytes between hypertrophic and/or proliferating cartilage cells within rather abundant cartilage matrix; hyperdense cancellous bone; trabeculae short, tortuous and irregular. Ingrowth of capillaries and osteoclastic activity appear normal (×112; Masson trichrome staining).

Fig. 9. Epiphyseal region of right femur: abnormalities similar to those in Figure 8. Some enlarged lacunae around resting cartilage cells in the vicinity of the severely abnormal enchondral ossification; lacunar enlargement without concomitant cellular hypertrophy; (×112; Masson trichrome).

The challenge of explaining fully the peculiarities of enchondral ossification in Blomstrand type chondrodysplasia must await the observation of more patients, preferably ones already identifiable antenatally with opportunity of obtaining more samples prospectively. Complementary studies in electronmicroscopy, in vitro cytology, and molecular biology are bound to elucidate the pathogenesis of this distinct osteochondrodysplasia and to help unravel some of the important steps in normal bone formation and skeletal growth.

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